GlaxoSmithKline
Scientific Office

جلاكسو سميث كلاين
المكتب العلمي

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June 26th, 2013

Title: TYKERB® (lapatinib ditosylate monohydrate) – Comparative data have shown that Lapatinib based regimens are less effective than trastuzumab based regimens in certain settings

Dear Healthcare Professional,

Summary

- Two recent trials have shown statistically significant superior efficacy of trastuzumab as compared to lapatinib.This effect was particularly pronounced in the patients who had no prior exposure to trastuzumab.
- Prescribers are reminded that Tykerb® should not be prescribed in combination with capecitabine unless patients have progressed on trastuzumab, in accordance with the licensed indication.

Action Being Taken by GlaxoSmithKline

The prescribing information for TYKERB will be updated to include information that in certain settings lapatinib-based regimens have shown to be less effective than trastuzumab-based regimens

GlaxoSmithKline is submitting to the Saudi Food and Drug Authority (SFDA) the updated TYKERB prescribing information to obtain SFDA approval.

Action required by Health Care Providers/Investigators

In view of the available data, Health Care Providers are reminded that Tykerb in combination with capecitabine is approved for patients with advanced or breast metastatic cancer whose tumours overexpress HER2/neu (ErbB2) with progression following prior therapy which must have included trastuzumab in the metastatic setting.

Further information on the efficacy concern

Recently, there have been results reported from pre-planned interim analyses from two comparative studies of Tykerb© in combination with chemotherapy versus Herceptin© (trastuzumab) in combination with chemotherapy in HER2 positive metastatic breast cancer patients.

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- CEREBEL(EGF111438) (N=540) is a randomised Phase III study comparing the effect of lapatinib in combination with capecitabine relative to trastuzumab in combination with capecitabine on the incidence of CNS as site of first relapse in women with HER2 positive metastatic breast cancer. Patients were stratified based on prior trastuzumab treatment (yes versus no) and number of prior treatments for metastatic disease (0 versus ≥1 line). There was superior efficacy with the trastuzumab plus capecitabine combination in terms of progression-free survival (PFS) and overall survival (OS) compared to the lapatinib plus capecitabine combination. Median PFS was 6.60 months in the lapatinib-containing arm compared with 8.05 months in the trastuzumab-containing arm (HR=1.30; 95%CI 1.04 to 1.64). The median OS was 22.7 months in the lapatinib-containing arm compared with 27.3 months in the trastuzumab-containing arm (HR=1.34 (95%CI 0.95 to 1.90). The results of the final analysis of Study EGF111438/CEREBEL, including subgroup analysis based on prior trastuzumab treatment, are presented in the table below:

Study EGF111438/CEREBEL: Kaplan-Meier Analyses of Investigator-Assessed Progression-Free Survival and Overall Survival (ITT population, final analysis)				
	Investigator-Assessed PFS [b]		**Overall Survival**	
	Lapatinib+ Capecitabine 2000 mg/m²/day	**Trastuzumab+ Capecitabine 2500 mg/m²/day**	**Lapatinib+ Capecitabine 2000 mg/m²/day**	**Trastuzumab+ Capecitabine 2500 mg/m²/day**
ITT population (All)				
N	271	269	271	269
Events, n (%)	160 (59)	134 (50)	70 (26)	58 (22)
Median, mo (95% CI)	6.60 (5.72, 8.11)	8.05 (6.14, 8.9)	22.7 (19.5, -)	27.3 (23.7, -)
HR (95% CI) [a]	1.30 (1.04, 1.64)		1.34 (0.95,1.90)	
Subjects who had received prior trastuzumab				
N	*167*	*159*	*167*	*159*
Events, n(%)	*103 (62)*	*86 (54)*	*43 (26)*	*38 (24)*
Median, mo (95% CI)	6.6 (5.7, 8.3)	6.1 (5.7, 8.0)	22.7 (20.1, -)	27.3 (22.5, 33.6)
HR (95% CI) [a]	1.13 (0.85, 1.50)		1.18 (0.76, 1.83)	
Subjects who had not received prior trastuzumab				
N	104	110	104	110
Events, n(%)	57 (55)	48 (44)	27 (26)	20 (18)
Median, mo (95% CI)	6.3 (5.6, 8.1)	10.9 (8.3, 15.0)	- (14.6, -)	- (21.6,-)
HR (95% CI) [a]	1.70 (1.15, 2.50)		1.67 (0.94, 2.96)	

Final analysis; based on data from a cut-off date of 11 June 2012.

CI = confidence interval; HR = hazard ratio; mo = months; PFS = progression free survival

a. Pike estimate of the treatment hazard ratio, <1 indicates a lower risk for lapatinib+capecitabine compared with trastuzumab+capecitabine

b. PFS was defined as the time from randomization to the earliest date of disease progression or death from any cause, or to the date of censor

- The second study , COMPLETE is a randomised Phase III study (EGF108919) (N=636) comparing the activity of lapatinib plus taxane followed by lapatinib alone versus trastuzumab plus taxane followed by trastuzumab alone as first line therapy for women with HER2 positive metastatic breast cancer. Tykerb® is not approved in combination with a taxane .

The study was stopped early due to superior efficacy of the trastuzumab plus taxane arm in terms of progression-free survival. Results from a pre-planned interim analysis showed that the PFS in the lapatinib-containing arm was lower than in the trastuzumab-containing arm (median PFS was 8.8 months in the lapatinib-containing arm compared with 11.4 months in the trastuzumab-containing arm; HR=1.33; 95% CI 1.06 to 1.67, p=0.01). The hazard ratio for OS was 1.1 (95% CI 0.75 to 1.61; p=0.62)), based on 18% (n=115) deaths.

The letter is sent in agreement with the Saudi Food and Drug Authority

Further Information

GlaxoSmithKline will continue to monitor the safety of Tykerb® (Lapatinib) and update SFDA of any serious adverse event for evaluation. You can assist us in monitoring the safety of Tykerb® (Lapatinib) by reporting adverse reactions to fax: +96626536660 or by email to GlaxoSmithKline safety email: faisal.m.shujrah@gsk.com Or to the National Pharmacovigilance and Drug Safety Center at Fax: +966-11-2057662 or by email to: npc.drug@sfda.gov.sa

If you have any question about the new information, please contact GSK medical information department at GlaxoSmithKline Saudi Arabia by phone: +966 2 6536666 or fax: +966 2 6536660.

Best regards

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References

1. Gelmon KA, Boyle F, Kaufman B, et al. Open-label phase III randomized controlled trial comparing taxane-based chemotherapy (Tax) with lapatinib (L) or trastuzumab (T) as first-line therapy for women with HER2+ metastatic breast cancer: Interim analysis (IA) of NCIC CTG MA.31/GSK EGF 108919. J Clin Oncol. 2012;30(suppl; abstr LBA671).
2. X Pivot, V Semiglazov, B Zurawsky, R Allerton, A Fabi, E Ciruelos, R Parikh, M DeSilvio, S Santillana and R Swaby : [CEREBEL (EGF111438): An open label randomized phase III study comparing the incidence of CNS metastases in patients(pts) with HER2+ Metastatic Breast Cancer (MBC), treated with Lapatinib plus Capecitabine (LC) versus Trastuzumab plus Capecitabine (TC).Ann Oncol (2012) 23(suppl 9): ixe5 abstract LBA11 doi:10.1093/annonc/mds499